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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/284,199	08/02/94	BURRELL	M 1130261CONT.
		18M2/1021	EXAMINER
			FOX, D
		ART UNIT	PAPER NUMBER
		1803	14
		DATE MAILED:	10/21/96

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

#### OFFICE ACTION SUMMARY

- Responsive to communication(s) filed on 8/2/96
- This action is FINAL.
- Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire — 3 — month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

- Claim(s) 2-4, 7-8, 13-16, 20-59 is/are pending in the application.
- Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- Claim(s) 20-21 is/are allowed.
- Claim(s) 2-4, 7-8, 13-16, 22-59 is/are rejected.
- Claim(s) \_\_\_\_\_ is/are objected to.
- Claims \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.
- The specification is objected to by the Examiner.
- The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

- Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- All  Some\*  None of the CERTIFIED copies of the priority documents have been received.
- received in Application No. (Series Code/Serial Number) 07/628,216.
- received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_.

- Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- Notice of Reference Cited, PTO-892
- Information Disclosure Statement(s), PTO-1449. Paper No(s). \_\_\_\_\_
- Interview Summary, PTO-413
- Notice of Draftsperson's Patent Drawing Review, PTO-948
- Notice of Informal Patent Application, PTO-152

- SEE OFFICE ACTION ON THE FOLLOWING PAGES -

Best Available Copy

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.129(a). Applicants' first submission after final filed on 2 August 1996 has been entered.

The application should be reviewed for errors. Errors appear, for example, on page 5 of the specification, line 8 of the second full paragraph, where "adenine" should be changed to --adenosine--.

Claims 2-4, 7-8, 13-16, 30-49, and 52-59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, and dependent claims 3-4, 7-8, 31-38, 47-49 and 58-59, are indefinite in the recitation in claim 2 of "whereby there is caused a modification of the amount of a metabolic intermediate in glycolysis or in a pathway for the synthesis or degradation of starch, sucrose or reducing sugar" (emphasis added) which is unduly narrative and alternative, and which fails to clearly set forth the required claim elements. Furthermore, the relationship of the phrase "or in a pathway..." to the preceding claim elements is unclear.

Claim 13, and dependent claims 14-16, 39-46 and 52, are indefinite in the recitation of "thus to cause..." for the reasons stated above.

Claim 30 and dependent claim 55 are indefinite in the recitation of part (b) of claim 30 for the reasons stated above. Furthermore, it is unclear whether "the pre-existing plant pathway" clause refers to the synthesis or degradation of starch, sucrose or reducing sugar. Finally, the claim is awkward in its recitation of "and of which" in lines 4-5 of part (b).

Claims 53-54 and dependent claims 56-57 are indefinite in the recitation of part (b) for the reasons stated above.

Claims 2-4, 7-8, 13-16, 22-30, 32-33, 35-38, 40-42 and 44-59 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a process for the introduction of a gene encoding either phosphofructokinase or adenosine diphosphoglucose pyrophosphorylase into the genome of a plant cell. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification only demonstrates the utilization of a gene encoding the glycolytic enzyme phosphofructokinase for plant transformation. In addition, the Burrell declaration submitted 25 March 1993 in parent application Serial No. 07/991,451 demonstrates the utilization of a gene encoding ADP glucose pyrophosphorylase. No guidance has been presented for the identification or isolation of other genes involved in glycolysis. It is unclear whether plant transformation with

genes encoding other glycolytic enzymes would alter glycolysis and/or kill the transformed plant cells and plants (see, e.g., page 3 of the specification, first full paragraph; page 3 of the ap Rees declaration filed 22 January 1993 in parent application Serial No. 07/991,451). It is also unclear whether plants transformed with more than one glycolytic gene would be adversely affected, given the "double dose" of glycolytic enzyme alteration.

Furthermore, von Schaewen et al. demonstrate the unpredictability inherent in the transformation of plants with genes encoding glycolytic enzymes. The transformation of tobacco resulted in dwarfing, bleaching and browning of leaves, and root stunting (see, e.g., page 3037). The lack of such deleterious effects on plant health in the potato plants transformed with the PFK gene has been previously argued by Applicants as evidence of unexpected results. Respiration, i.e. glycolysis, was also inhibited (see, e.g., page 3039, column 1, bottom paragraph). Furthermore, the transformation of a different plant species by von Schaewen et al. resulted in a completely different response to the introduction of a glycolytic gene, i.e. lack of appreciable change in phenotype or starch content (see, e.g., page 3038, column 1, top paragraph; page 3039, column 2, bottom paragraph).

Thus, undue experimentation would be required by one skilled in the art to identify and isolate the gene or genes which encode

any other glycolytic enzyme, and to evaluate the effects of said gene(s) on transformed plant cells and plants; given the unpredictability inherent in the process as discussed supra; the lack of guidance regarding the identification, isolation and characterization of the gene(s) encoding any other glycolytic enzyme; and the breadth of the claims which encompass either eight divergent enzymes or a multitude of unspecified enzymes involved in either glycolysis or the synthesis or degradation of a variety of carbohydrates.

See Ex parte Forman, 230 USPQ 546, 547 (PTO Bd. App. Int. 1986), where it was taught that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims."

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --  
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30 and 53-57 are rejected under 35 U.S.C. § 102(b) as being anticipated by Grill et al. (WO 89/08145). Grill et al. teach potato transformation with a viral vector containing a chimeric gene comprising a viral coat protein promoter and a bacterial cyclodextrin glucotransferase gene which encodes two forms of a starch degrading enzyme (see, e.g., pages 37-39; pages 49-51). Tubers and seeds produced by the plants would also contain the chimeric gene. The screenable GUS marker gene (page 45) comprises the gene encoding a second enzyme.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 30, 54-55 and 57 are rejected under 35 U.S.C. § 103 as being unpatentable over Houck et al. (WO 88/09334) taken with Gay et al.

Houck et al. teach the obtention of a tomato fruit-specific promoter and plant transformation with a chimeric gene comprising

the promoter and a structural gene (see, e.g., paragraph bridging pages 11 and 12; pages 24-26; page 29). Houck et al. also suggest the use of the fruit-specific promoter for the expression of a heterologous sugar degrading enzyme, such as levansucrase, for varying the fruit phenotype (see, e.g., page 6, lines 25-31). A selectable antibiotic resistance marker gene such as the kanamycin resistance gene employed by Houck et al. could comprise the gene encoding a second enzyme, as is well known in the art.

Houck et al. do not teach plant transformation with a plant expressible promoter and a gene encoding sugar degradation.

Gay et al. teach the cloning of a bacterial levansucrase gene, and the expression of this gene in a heterologous host (see, e.g., page 1427, column 1, first full paragraph; page 1428, column 2, second paragraph). Gay et al. also teach the probable existence of an alternative form of the enzyme before cleavage of a signal peptide (see, e.g., page 1429, column 2, first full paragraph).

It would have been obvious to one of ordinary skill in the art to utilize the method of tomato transformation with a fruit-specific promoter and structural gene as taught by Houck et al., and to modify that method by incorporating the levansucrase gene taught by Gay et al., given the suggestion to do so by Houck et al. and the recognition by those of ordinary skill in the art that each would have continued to function in its known and expected manner. Thus, the claimed invention was clearly prima facie

facie obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

Claims 2-4, 7-8, 13-16, 20-29, 31-52 and 58-59 are deemed free of the prior art, in view of the unpredictability inherent in the process as discussed above, and further in view of the failure of the prior art to teach or suggest the obtained effects following plant transformation with the exemplified genes, as stated in the last office action for claims 20 and 25-29.

Claims 31, 34, 39 and 43 would be allowable if rewritten to overcome the rejection under 35 U.S.C. 112 and to include all of the limitations of the base claim and any intervening claims.

Claims 20-21 are allowed, as stated in the last office action for claim 20.

Applicants urge that rejection of the claims under 35 USC 112, first paragraph, is improper, given the previous isolation of the claimed genes as evidenced by literature citations appended to the Burrell declaration of 2 August 1996, the demonstration von Schaewen et al. of the claimed effects following transformation with the acid invertase gene, the ability of the skilled artisan to select transformed plants which did not exhibit deleterious effects, and Applicants' transformation with antisense acid invertase or sucrose-phosphate-synthase constructs and a sense sucrose synthase construct as evidenced by the Burrell declaration of 2 August 1996.

The Examiner maintains that von Schaewen et al. demonstrate deleterious effects on plant health following transformation with the acid invertase gene, as well as variability both within and between plant species, thus demonstrating the unpredictability inherent in the process. Applicants' specification does not provide any guidance regarding the transformation or evaluation of plants with non-exemplified genes. Furthermore, the claims are broadly drawn to any plant species, at least eight genes, and in several instances any gene (claims 30 and 53-57).

Applicants' assertions that the skilled artisan could select unaffected plants are not deemed persuasive, particularly as it is unclear whether the unaffected plants possessed the introduced gene, exhibited expression of the gene, or would exhibit changes in sugar and starch content.

Applicants' results following transformation with antisense invertase or sucrose-phosphate-synthase constructs, or sense sucrose synthase constructs, are not deemed probative. The claims are not drawn to antisense constructs, so that the applicability of this data is unclear. Furthermore, the specification is completely silent with respect to the design or evaluation of antisense constructs. Given the unpredictability inherent in antisense RNA-mediated gene regulation regarding lack of consistency of effective gene region (see, e.g., Chang et al., page 2347, column 1, first full paragraph), the lack of correlation between amount of antisense transcript and level of

gene inhibition (see, e.g., Sheehy et al., page 8808, column 1, top paragraph; paragraph bridging pages 8808 and 8809), and the lack of reduction in phenotypic expression (see, e.g., Smith et al., page 725, column 2, top paragraph); the lack of guidance in the specification regarding the construction or evaluation of antisense constructs; and the breadth of the claims as discussed supra; undue experimentation would have been required by one skilled in the art to obtain and evaluate plants transformed with antisense RNA-encoding constructs.

With respect to Applicants' results regarding sucrose synthase, the specification provides no guidance regarding the isolation of this gene. The list of references accompanying the Burrell declaration of 2 August 1996 was not accompanied by the references themselves. The reference regarding sucrose synthase appears to have genetically identified the gene in terms of an inheritance pattern, but does not appear to have taught the chromosomal location of the gene or its isolation. In addition, the references regarding pyrophosphate fructose 6-P phosphotransferase and sucrose phosphate synthase only appear to demonstrate the isolation of the protein encoded by the genes, without furnishing any information regarding the gene itself, let alone the isolation of the gene. See In re Bell, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and In re Deuel, 34 USPQ2d, 1210 (Fed. Cir. 1995), which teach that the mere existence of a

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protein does not enable claims drawn to a nucleic acid encoding that protein.

Thus, Applicants' results for non-exemplified genes involve antisense techniques and particular isolated genes which were not taught in the specification. Accordingly, the specification is not enabling for these non-exemplified genes, given the unpredictability inherent in the process as discussed above.

Applicants urge that the rejections of the claims under 35 USC 102 or 103 set forth above are improper, given the failure of the references to teach genes involved in a pre-existing metabolic pathway. The Examiner maintains that the rejected claims are not so limited. In claim 30, there is no clear requirement for a pre-existing metabolic pathway for the synthesis or degradation of carbohydrates. In claims 53-57, there is no recitation of this requirement at all.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David T. Fox whose telephone number is (703) 308-0280. The examiner can normally be reached on Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Douglas Robinson, can be reached on Monday through Friday at (703) 308-2897.

The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October 16, 1996

DAVID T. FOX  
PRIMARY EXAMINER  
GROUP 180

*David T. Fox*